

**EXHIBIT A**

**PATENT APPLICATION**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application

Confirmation No. 1192

Inventor(s) Corbett et al

Group: 1656

Application No. 10/816,708, filed Apr. 2, 2004  
(Case Docket No. 20892 US2)

Examiner: A. Kim

For: **CRYSTALS OF GLUCOKINASE AND METHODS OF GROWING THEM**

**PRELIMINARY AMENDMENT, RCE AND PETITION FOR EXTENSION OF TIME**

Nutley, New Jersey 07110  
July 31, 2008

Mail Stop: Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

This RCE and Preliminary Amendment and response is in response to the Advisory Action mailed July 17, 2008, and in response to the Final Office Action mailed April 14, 2008, in connection with the above-identified patent application. Applicants respectfully request a one (1) month extension of time. With the extension of time, this Amendment is timely filed. Entry of this Amendment is earnestly requested to place this case into condition for allowance.

In response to the Advisory Action mailed July 17, 2008, and the Final Office Action mailed April 14, 2008, Claims 1-4 are pending and stand rejected. Claims 1-4 have been amended.

Accordingly, please amend the above-identified application as follows:

**In the Claims:**

5. (Currently Amended) A co-crystal of mammalian Glucokinase (Seq-ID-NO:1) (SEQ ID NO:1) and a ligand bound to an allosteric site of the Glucokinase, wherein

the co-crystal has unit cell dimensions of:

a and b are from 79 Å to 80.2 Å;

c is from 318 Å to 325 Å;

$\alpha$  and  $\beta$  are 90°; and

$\gamma$  is 120°;

and the co-crystal has P6(5)22 symmetry, wherein further the ligand is selected from the group consisting of 3-Cyclopentyl-2-pyridin-4-yl-N-thiazol-2-yl-propionamide, N-(5-Bromo-pyridin-2-yl)-2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionamide, 2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide, (2S)-2-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester, (2S)-[2-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-thiazol-5-yl]-oxo-acetic acid ethyl ester, (2S)-[3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido]-acetic acid methylester, (2S)-1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea, and (2S)-[3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido]-acetic acid ethyl ester.

6. (Currently Amended) A crystal of mammalian Glucokinase (Seq-ID-NO:1) (SEQ ID NO:1), wherein

the crystal has unit cell dimensions of:

a and b are from 79 Å to 80.2 Å;

c is from 318 Å to 325 Å;

$\alpha$  and  $\beta$  are 90°; and

$\gamma$  is 120°;

and the crystal has P6(5)22 symmetry.

7. (Currently Amended) A process for co-crystallizing mammalian Glucokinase (Seq-ID NO:1) (SEQ ID NO:1) and an allosteric ligand of Glucokinase, the process comprising:

providing a buffered, aqueous solution of 9 to 22 mg/ml of the mammalian Glucokinase (SEQ ID NO:1);

adding a molar excess of the allosteric ligand to the aqueous solution of mammalian Glucokinase; and

growing crystals by vapor diffusion using a buffered reservoir solution of 16% to 25% PEG, 0% w/v to 30% w/v glucose and 8 to 10 mM DTT, wherein the PEG has an average molecular weight of about 8,000 to about 10,000-, wherein further the ligand is selected from the group consisting of 3-Cyclopentyl-2-pyridin-4-yl-N-thiazol-2-yl-propionamide, N-(5-Bromo-pyridin-2-yl)-2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionamide, 2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide, (2S)-2-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester, (2S)-2-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-thiazol-5-yl]-oxo-acetic acid ethyl ester, (2S)-[3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido]-acetic acid methylester, (2S)-1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea, and (2S)-[3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido]-acetic acid ethyl ester.

8. (Currently Amended) The process of claim 3, wherein the step of growing crystals by vapor diffusion comprises:

streaking the buffered, aqueous solution of mammalian Glucokinase (Seq-ID NO:1) (SEQ ID NO:1) with added allosteric ligand on a surface to form an elongated droplet of protein solution, and

streaking about an equal amount of the buffered reservoir solution across the elongated droplet of protein solution, forming a combined droplet shaped like the letter 'X'.

### **REMARKS**

In response to the Advisory Action mailed July 17, 2008, and the Final Office Action mailed April 14, 2008, Claims 1-4 are pending and stand rejected. Claims 1-4 have been amended. Support for the amendments may be found generally throughout the specification and specifically within paragraphs 8, 10, 23, 28, and 40-58 inclusive. No new matter has been added by virtue of these amendments.

#### **III. Claim Objections**

Applicants have amended the specification to capitalize the term SEQ ID NO: 1 in Claims 1-4 as per the Examiner's suggestion.

Accordingly, Applicants respectfully request that the objections to Claims 1-4 be hereby withdrawn. Applicants further note that Claim 2, as amended, is free of any pending rejections in the April 14, 2008 Office Action, and thus Applicants respectfully request Claim 2 be placed into condition for allowance.

#### **IV. Claim Rejections**

##### **C. 35 USC 112, 1<sup>st</sup> paragraph, written description**

Claims 1 stands rejected by the Examiner under 35 USC 112, 1<sup>st</sup> paragraph for lack of written description. Specifically, the Examiner contends that the ligand bound to the disclosed, otherwise adequately structurally described, crystal should be disclosed in said claim. Applicants respectfully traverse and overcome said rejection.

Applicants have amended Claim 1 to define the ligand to be bound to the disclosed crystal as being selected from the group of ligands described in Examples 3-10 of the specification. The Examiner has acknowledged enablement for these Examples and the ligands described therein. Applicants accordingly respectfully submit that Claim 1, as amended, is therefore clear and adequately-defined and described.

Applicants therefore respectfully request that the 35 USC 112, 1<sup>st</sup> paragraph rejection for written description be withdrawn and that Claim 1, as herein amended, be placed into condition for allowance.

D. 35 USC 112, 1<sup>st</sup> paragraph, enablement

Claims 1 and 3-4 stand rejected by the Examiner under 35 USC 112, 1<sup>st</sup> paragraph for lack of enablement. Specifically, the Examiner contends there is no enablement for all the crystals of Claim 1 and methods preparation of same in Claims 3-4. The Examiner does acknowledge enablement of crystals comprising Seq ID No:1 and enablement for methods of preparing crystals of Seq ID No:1 with or without specified ligands (Examples 3-10 of the specification). Applicants respectfully traverse and overcome said rejection.

As noted ante, Applicants have amended Claim 1 to define the ligand to be bound to the disclosed crystal as being selected from the group of ligands described in Examples 3-10 of the specification. Applicants have likewise amended Claim 3 similarly to include the group of ligands described in Examples 3-10 of the specification. The Examiner has acknowledged enablement for these Examples and the ligands described therein.

Therefore, Applicants respectfully submit that Claims 1 and 3-4, as herein amended, are enabled by the specification. Accordingly, Applicants respectfully request that the 35 USC 112 1<sup>st</sup> paragraph enablement rejection be hereby withdrawn and Claims 1 and 3-4, as amended, be placed into condition for allowance.

No further fee is believed to be required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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# Request for Continued Examination (RCE) Transmittal

Address to:  
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P.O. Box 1450  
Alexandria, VA 22313-1450

Application Number	10/816,708
Filing Date	04/02/2004
First Named Inventor	Wendy Lea Corbett
Art Unit	1656
Examiner Name	
Attorney Docket Number	20892 US2

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application. This request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 CFR 1.114** Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

- a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
- i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on \_\_\_\_\_
- ii. ☐ Other \_\_\_\_\_
- b. ☒ Enclosed
- i. ☒ Amendment/Reply
- iii. ☐ Information Disclosure Statement (IDS)
- ii. ☐ Affidavit(s)/ Declaration(s)
- iv. ☐ Other \_\_\_\_\_

## 2. Miscellaneous

- a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of \_\_\_\_\_ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(f) required)
- b. ☐ Other \_\_\_\_\_

## 3. Fees

- The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
- The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to
- a. ☒ Deposit Account No. 08-2525. I have enclosed a duplicate copy of this sheet.
- i. ☒ RCE fee required under 37 CFR 1.17(e) **(\$810.00)**
- ii. ☒ Extension of time fee (37 CFR 1.136 and 1.17)
- iii. ☐ Other \_\_\_\_\_
- b. ☐ Check in the amount of \$ \_\_\_\_\_ enclosed
- c. ☐ Payment by credit card (Form PTO-2038 enclosed)

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## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Robert Hoag/	Date	July 31, 2008
Name (Print/Type)	Robert Hoag	Registration No.	39,712

## CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

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